Serum Lipid Changes during Acitretin (Etretin) Treatment of Psoriasis and Palmo-plantar Pustulosis

CARIN VAHLQUIST,[1] INGEMAR SELINUS[2] and BENGT VESSBY[2]

Departments of [1]Dermatology and [2]Geriatrics, University Hospital, Uppsala, Sweden

Vahlquist C, Selinus I, Vessby B. Serum lipid changes during acitretin (etretin) treatment of psoriasis and palmo-plantar pustulosis. Acta Derm Venereol (Stockh) 1988; 68:300–305.

The effects of acitretin (free acid of etretinate) on the serum lipoprotein pattern and on the fat elimination in serum of 8 patients with psoriasis and 4 with palmo-plantar pustulosis were studied. The drug was given for 12 weeks; the average daily dose was 40 mg. Lipoprotein analyses and an intravenous fat tolerance test (IVFTT) were performed on three occasions (before, after 8 weeks' treatment, as well as 8 weeks after the end of the treatment). Acitretin increased the triglyceride concentration of the very low density lipoproteins by about 50% ($p<0.02$) and reduced the cholesterol of the high density lipoproteins significantly ($p<0.001$), leading to an increased low density/high density lipoprotein cholesterol ratio ($p<0.02$). The IVFTT indicated a lowering of the fat elimination capacity. All changes reverted to the original values after an 8-week wash-out period. The data suggest that the effects of acitretin on the lipoprotein metabolism resemble those of etretinate and isotretinoin.
(Received February 17, 1988.)

C. Vahlquist, Department of Dermatology, University Hospital, S-751 85 Uppsala, Sweden.

It has long been known that etretinate and isotretinoin, the two most frequently used synthetic retinoids, both exert an unfavourable influence on the serum lipid pattern. Thus, concentrations of both very low density lipoprotein triglycerides (VLDL-TG) and low density lipoprotein cholesterol (LDL-CHOL) increase, while high density lipoprotein cholesterol (HDL-CHOL) decreases (for review, see 1–3). The magnitude of the lipid changes varies between individuals and pathological values are rare. It is becoming increasingly clear, however, that even moderate increases in serum triglycerides and LDL-CHOL over a prolonged period of time may augment the risk for developing atherosclerosis (4, 5) as may probably also low HDL concentrations (6). It was thus of interest to investigate the effects of various synthetic retinoids on serum lipid levels.

Acitretin, the main active metabolite of etretinate, has the advantage of being less hydrophobic and thus not stored in the adipose tissue to the same extent as the parent compound. As a result, the terminal half-life of acitretin is approximately 50 h as compared with 100 days for etretinate (for review, see 7). Clinically, the most important implication is that the period in which women of child-bearing potential are exposed to the risk of retinoid-induced teratogenicity, is considerably shorter after acitretin therapy than after etretinate therapy. Since preliminary data also suggest that acitretin is clinically equivalent to etretinate (8), the former is anticipated to replace etretinate within the near future.

However, the side effects of acitretin have not yet been adequately investigated. So far, only preliminary data on the effects of acitretin on the blood lipids have been reported (8). Therefore, as part of a multicentre study on acitretin therapy for psoriasis, the clinical results of which will be presented separately (Kragballe et al., to be published), we now report the effects of the drug on the serum lipoprotein pattern and on the results of an intravenous fat tolerance test (IVFTT) in a subset of 12 patients.

PATIENTS AND METHODS

Patients

After giving informed consent 12 patients, 5 men and 7 women, entered the study. Eight of them had psoriasis and 4 had palmo-plantar pustulosis (PPP). The mean duration of the patients' disease was 13.3 years (range 2–33 years). Their mean age was 51.5 years (range 42–61 years). Three of the women were younger than 50 years, one of these used an IUD as contraceptive, one was sterile and one lived in celibacy.

The mean body-weight of the patients was 77.9 kg (range 60–101 kg). Their mean Broca's index was 1.14 (range 0.73–1.35) (Broca's index = weight (kg)/height (cm) −100). One woman and one man with psoriasis had a mild diabetes, treated with glipzide and glibenclamide. The other patients had no diabetes, thyroid disease or any other known disorder associated with lipoprotein disturbances. One patient had taken etretinate intermittently until one month before entering the study. The other patients, who had used etretinate earlier, had not taken the drug for 2 months or more before the start of the study. The patients were requested not to change their dietary habits during the study.

Lipid analyses

Triglycerides (TG) and cholesterol (CHOL) in whole serum as well as in the different lipoprotein fractions: very low density lipoprotein (VLDL), low density lipoprotein (LDL) and high density lipoprotein (HDL) were analysed. Lipoprotein lipid concentrations were determined after an overnight fast (at 8 a.m.). VLDL, LDL and HDL were isolated with a combination of preparative ultracentrifugation at d=1.006 (9) and precipitation from the bottom fraction with a sodium phosphotungstate and magnesium chloride solution (10). Triglyceride and cholesterol concentrations were determined in serum and in the isolated lipoprotein fractions by enzymatic methods using Boehringer-Mannheim (Munich, FRG) kits 126012 and 124087, modified for use in a Multistat III F/LS apparatus (Instrumentation Laboratories, Lexington, Mass., USA).

The concentrations of serum apolipoproteins (apo)B, A-I and A-II were determined by turbidimetry in the Multistat III F/LS apparatus using monospecific polyclonal antibodies against apo-B, A-I an A-II, respectively. Before assay the samples were preincubated with triglyceride lipase as suggested by DaCol & Kostner (11).

An intravenous fat tolerance test (IVFTT) was performed *ad modum* Carlson & Rössner (12). This test shows the individual's capacity to remove intravenously injected fat from the circulation, expressed as the fractional removal rate of Intralipid® (K_2, % per minute). A K_2 value above 4% per minute is considered normal.

Design of the study

The analyses were performed on 12 patients, included in a Scandinavian multicentre study on 100 patients with severe psoriasis or PPP. The daily dose of acitretin was 40 mg during the first 4 weeks of treatment. The dose was adjusted according to the therapeutic results and the clinical side effects.

The patients were treated for 12 weeks. Lipid analyses were performed before the treatment started, after 8 weeks' treatment and after an 8 week wash-out period, i.e. in the 20th week of the study. Haemoglobin, white blood cell count, blood sugar, bilirubin, creatinine, alkaline phosphatases, aspartate aminotransferase (ASAT) and alanine aminotransferase (ALAT) were checked every 4 weeks.

Statistics

The equality of period means has been analysed in a two-way analysis of variance model with factors for patient and periods.

RESULTS

Twelve patients entered the study. All completed the investigation in accordance with the schedule. In 4 out of the 12 patients, the acitretin dosage was reduced after 4 weeks' treatment, to 30 mg per day and in 3 patients the dose was increased to 50–60 mg per day. The other patients had a constant dose of 40 mg per day throughout the 12-week treatment period. One male patient suffered a transient hepatotoxic reaction that was probably drug-induced (Vahlquist, C., to be published). His serum lipid values were unremarkable, however, and are not excluded below. The other patients were healthy during the study and did not reveal any pathologic routine blood tests.

Table I. *Concentrations (mmol/l) of triglycerides (TG) and cholesterol (CHOL) in whole serum and in the different density fractions (VLDL, LDL, HDL); LDL/HDL represents the cholesterol ratio of these fractions; mean values ± SD*

	Whole serum		VLDL		LDL		HDL		
	TG	CHOL	TG	CHOL	TG	CHOL	TG	CHOL	LDL/HDL
Before treatment (0 weeks)	1.76 ±0.69	5.64 ±1.27	1.02 ±0.56	0.44 ±0.23	0.53 ±0.19	4.04 ±1.09	0.21 ±0.08	1.20 ±0.30	3.44 ±0.86
During treatment (8 weeks)	2.38 ±1.28	5.68 ±1.20	1.54 ±1.14	0.64 ±0.41	0.59 ±0.20	3.98 ±0.89	0.24 ±0.09	1.09 ±0.29	3.77 ±0.88
After wash-out (20 weeks)	1.98 ±0.77	5.68 ±1.13	1.15 ±0.74	0.47 ±0.27	0.59 ±0.26	4.07 ±0.97	0.25 ±0.10	1.18 ±0.31	3.57 ±0.96
Significance of difference (0–8 weeks) *P*	≤0.01	NS	<0.02	<0.01	NS	NS	NS	<0.001	≤0.02

Lipid changes

The TG and CHOL levels in whole serum and in the different lipoprotein fractions as well as the LDL/HDL-CHOL ratios during the study are presented in Table I.

Whole serum: The mean concentration of TG was significantly elevated after 8 weeks treatment, compared with the pretreatment value. The individual values returned to pretreatment levels during the wash-out period. The mean serum CHOL concentration did not exhibit any significant change during the study.

Lipoproteins: The TG and CHOL concentrations of the VLDL fraction increased significantly during 8 weeks of treatment. The LDL fraction showed no significant changes. By contrast, there was a marked decrease in HDL-CHOL at 8 weeks. The HDL-TG remained unchanged throughout the study. All values returned to about pretreatment levels during the wash-out period.

Ratio of CHOL in LDL/HDL: The mean LDL/HDL-CHOL ratio increased significantly ($p<0.02$) during acitretin treatment but generally returned to the original values during the wash-out (Table I). The individual changes of the LDL/HDL ratio varied greatly (Fig. 1).

Apo-lipoproteins: The apolipoproteins (apo-B, apo-AI and apo-AII) did not change significantly during the study (data not shown).

Intravenous fat tolerance test (IVFTT)

One patient was excluded from the evaluation of the IVFTT because of a technical mishap at the 8-week observation point. The remaining 11 patients' individual changes in K_2 are illustrated in Fig. 2. As can be seen, there is a statistically non-significant ($p<0.1$) decrease in the mean K_2-value, from 4.9%, before treatment, to 4.0% after 8 weeks of treatment. In general, there was a negative correlation between the individual K_2 and VLDL-TG values (Fig. 3). In 3 patients, the increase in the K_2-value was accompanied by a corresponding decrease in the VLDL-TG level. The values tended to revert to the pre-treatment levels during the wash-out period. If the values for drug-free periods are pooled, the mean value (5.1±2.0%) is significantly higher than the value at 8 weeks ($p<0.05$).

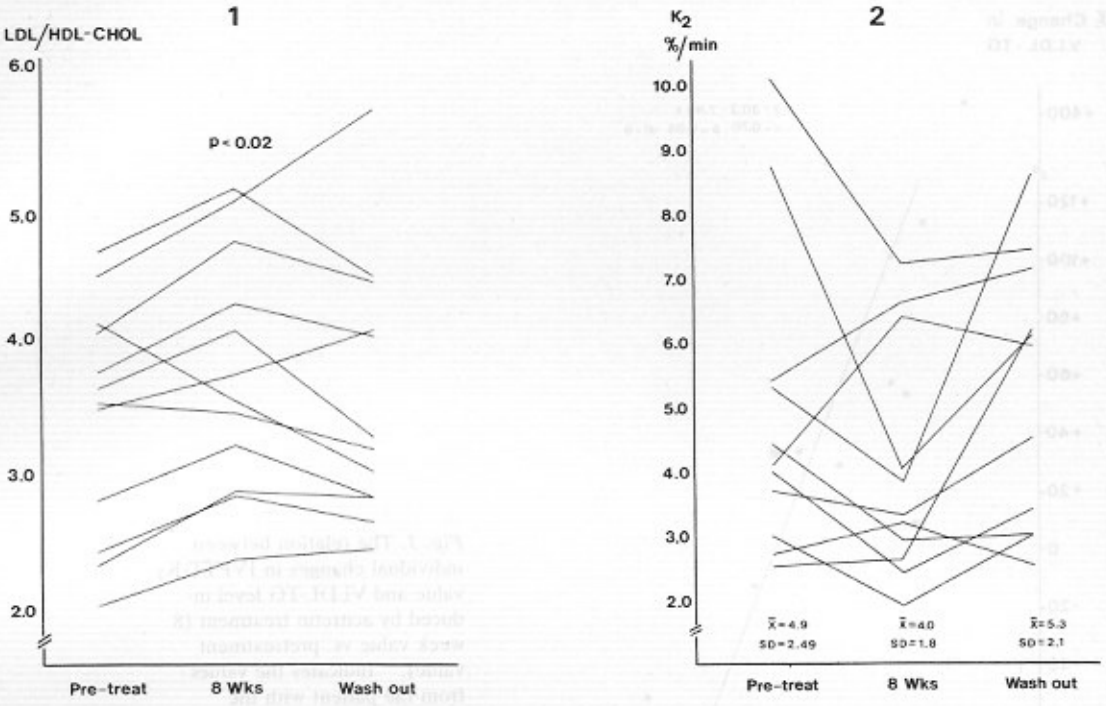

Fig. 1. Individual LDL/HDL-cholesterol ratios from 3 occasions: pretreatment, after 8 weeks' treatment and after 8 weeks' wash-out. The mean ± SD values and significances of difference are given in Table I.

Fig. 2. Individual K_2-values (fractional removal rate) of the intravenous fat tolerance test (IVFTT) from 3 occasions: pretreatment, after 8 weeks' treatment and after 8 weeks' wash-out. K_2 (%/min) is the fractional fat removal rate. Mean values and SD of 11 patients (see text) are presented in the figure.

DISCUSSION

The study shows that acitretin induces serum lipid changes that are similar in character and magnitude to those previously reported for etretinate (13, 14). The conclusion is also supported by our findings in 4 etretinate-treated patients who took part in the multi-centre study as double-blind controls (results not shown). These patients received 40 mg of etretinate and their mean serum TG value increased by 17% after 8 weeks as compared with 35% in the acitretin group. The serum CHOL values did not change significantly during the treatment period, in either group. The apparent invariance of the serum CHOL levels is spurious, however. It conceals an important redistribution of CHOL between the lipoproteins, most notably a decrease in HDL-CHOL, leading to a significant increase in the LDL/HDL-CHOL ratio. This ratio, the so-called atherogenic index, has been shown epidemiologically to be directly correlated to the risk of developing cardiovascular disease (15).

In the acitretin group, the LDL/HDL-CHOL ratio increased by 10% ($p<0.02$) vis-à-vis 22% in the etretinate group (data not shown) and 14% in a previous study on etretinate (14). A further advantage of the analysis of serum lipids by ultracentrifugation is that it demonstrates that the VLDL fraction is largely responsible for the increase in TG. The increase in VLDL-TG observed in the present study is greater than that in a previous study of etretinate, but comparable to that produced by isotretinoin (14). However, the individual response is variable and the magnitude of lipid changes in two groups of patients receiving identical treatment may differ considerably. Thus the final assessment of the relative potency of aci-

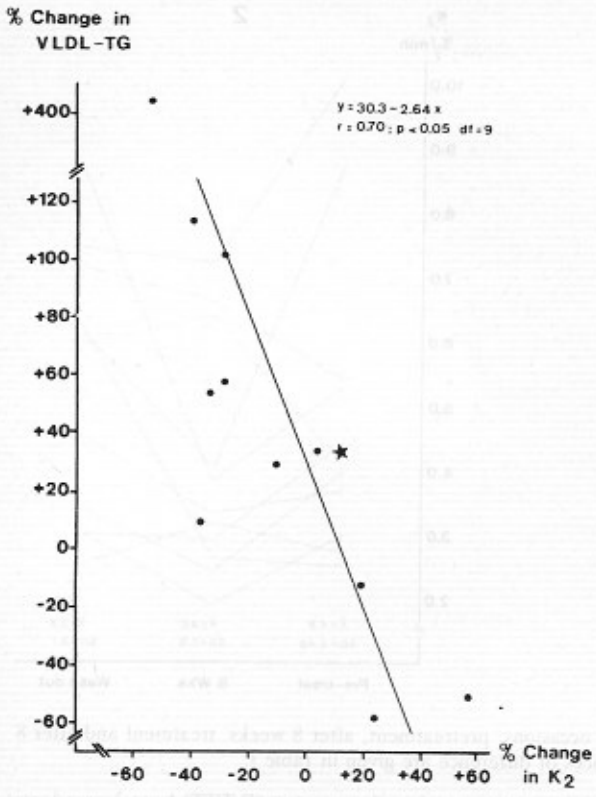

Fig. 3. The relation between individual changes in IVFTT-K_2 value and VLDL-TG level induced by acitretin treatment (8 week value vs. pretreatment value). * Indicates the values from the patient with the hepatotoxic reaction (see main text).

tretin and etretinate as inducers of hyperlipidemia must await the results of a proper cross-over study in which clinically equipotent doses of the two drugs are applied.

The mechanisms behind the lipid changes are still largely unknown, but most probably, acitretin interferes with the complex lipoprotein metabolism in the same manner as etretinate and isotretinoin. In support of this, acitretin was found to depress the ability to eliminate intravenously injected fat (IVFTT) and the reduction in the mean K_2 value was similar in acitretin (Fig. 2) and etretinate treated patients (data not shown).

The lowering of the IVFTT could be the result of an inhibition of the muscle lipoprotein lipases comparable to that observed earlier during isotretinoin and etretinate treatment (16). Theoretically, the drug might also alter the configuration of the lipoprotein particles, rendering them less apt to bind to the cellular lipoprotein receptors, thereby reducing the elimination rate for VLDL-TG. Studies are underway to elucidate such a possibility.

According to some investigators (17), retinoids also enhance the endogenous synthesis of VLDL particles in the liver. The similar lipid changes described as a result of treatment with acitretin (this study) or etretinate (13) are perhaps not surprising in view of the fact that etretinate is probably converted in vivo to acitretin (7). In conclusion, we feel that acitretin, when eventually introduced on the market, will probably produce the same pattern of serum lipid-associated side effects as etretinate.

ACKNOWLEDGEMENTS

We wish to thank Mrs Christina Rylander, Roche Products, Sweden for valuable support and Dr Gerd Michaëlsson and Dr Anders Vahlquist for stimulating discussions.

REFERENCES

1. Marsden J. Hyperlipidemia due to isotretinoin and etretinate: possible mechanisms and consequences. Br J Dermatol 1986; 114: 401–407.
2. Melnik B, Bros U, Plewig G. Evaluation of the atherogenic risk of isotretinoin-induced and etretinate-induced alterations of lipoprotein cholesterol metabolism. J Invest Dermatol 1987; 88: 39–43.
3. Vahlquist A, Vahlquist C. Etretinate and blood lipids—acute and long-term effects. Anglo-Nordic Symposium. Long-Term Treatment of Psoriasis. Helsinki, 1986. Proceedings 1986; 41–46. Horsmanheimo M, Kanerva L, Lauharanta J, Mustakallio K, Pitkänen H, eds.
4. Åberg H, Lithell H, Selinus I, Hedstrand H. Serum triglycerides are a risk factor for myocardial infarction but not for angina pectoris—results from a 10-year follow-up of Uppsala Primary Preventive Study. Atherosclerosis 1985; 54: 89–97.
5. Goldstein J, Brown M. The low-density lipoprotein pathway and its relation to atherosclerosis. Ann Rev Biochem 1977; 46: 897–930.
6. Gordon T, Castelli W, Hjortland M, Kannel W, Dawber T. High density lipoprotein as a protective factor against coronary heart disease: the Framingham Study. Am J Med 1977; 62: 707–714.
7. Vahlquist A, Rollman O. Clinical pharmacology of 3 generations of retinoids. Dermatologica 1987; 175 suppl: 20–27.
8. Camenzind M, Geiger J. Saurat J. Clinical efficacy of Ro 10-1670, the main metabolite of Tigason®. A pilot study in psoriasis. Retinoids: New Trends in Research and Therapy. Retinoid Symp. Geneva, 1984. Saurat ed. Basel: Karger, 1985; 305–308.
9. Havel R, Eder H, Bragdon J. The determination and chemical composition of ultracentrifugally separated lipoproteins in human serum. J Clin Invest 1955; 34: 1345–1353.
10. Siegler L, Wu W. Separation of serum high-density lipoprotein for cholesterol determination: ultracentrifugation vs. precipitation with sodium phosphotungstate and magnesium chloride. Clin Chem 1981; 27: 834–841.
11. DaCol P, Kostner G. Immunoquantification of total apolipoprotein B in serum by nephelometry: Influence of lipase treatment and detergents. Clin Chem 1983; 29: 1045–1050.
12. Carlson L, Rössner S. A methodological study of an intravenous fat tolerance test with Intralipid® emulsion. Scand J Clin Lab Invest 1972; 29: 271–280.
13. Michaëlsson G, Bergqvist A, Vahlquist A, Vessby B. The influence of "Tigason" (Ro 10-9359) on the serum lipoproteins in man. Br J Dermatol 1981; 105: 201–205.
14. Vahlquist C, Michaëlsson G, Vahlquist A, Vessby B. A sequential comparison of etretinate (Tigason®) and isotretinoin (Roaccutane®) with special regard to their effects on serum lipoproteins. Br J Dermatol 1985; 112: 69–76.
15. Wilson P, Garrison R, Castelli W, Feinleib M, McNamara P, Kannel W. Prevalence of coronary heart disease in the Framingham Offspring Study: Role of lipoprotein cholesterols. Am J Cardiol 1980; 46: 649–654.
16. Vahlquist C, Lithell H, Michaëlsson G, Selinus I, Vahlquist A, Vessby B. Plasma fat elimination, tissue lipoprotein lipase activity and plasma fatty acid composition during sequential treatment with etretinate and isotretinoin. Acta Derm Venereol (Stockh) 1987; 67: 139–144.
17. Marsden J, Laker M, Shuster S. Biochemical effects of isotretinoin. Retinoids: New Trends in Research and Therapy. Retinoid Symp. Geneva 1984. Saurat, ed. Basel: Karger, 1985; 461–465.